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EXPERIMENTAL PHYSIOLOGICAL STUDIES

with

LYSERGIC ACID DIETHYLAMIDE

(LSD – 25)

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EXPERIMENTAL PHYSIOLOGICAL STUDIES WITH LYSERGIC ACID DIETHYLAMIDE (LSD-25)

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STOLL[1] studied the effects of lysergic acid diethylamide (LSD-25) in both psychotic and normal subjects. Condrau[2] and others reported their results of administration of lysergic acid diethylamide to various types of subjects and in general confirmed the findings of Stoll.

For details of the chemistry of the ergot alkaloids, we refer to a more recent, comprehensive work by Stoll.[3] It should be mentioned in passing that all lysergic acid alkaloids have lysergic acid as a base. This substance is a multiple, active, polycyclic, nitrogenous carboxylic acid, which so far has not been synthesized. The natural ergot alkaloids contain *d*-lysergic acid and may be divided into two groups—the ergotamine-ergotoxine group, on the one hand, and the ergonovine group, on the other. In the former group *d*-lysergic acid is combined with a manifold peptid, whereas the latter group comprises the mono acid amides of the *d*-lysergic acid. Of this group only one natural representative is known, ergonovine, or *d*-lysergic acid-1-isopropanolamide. The substance under study (LSD) is *d*-lysergic acid diethylamide, the synthetic amide of the organic *d*-lysergic acid with a secondary amine, diethylamine. It, therefore, belongs to the ergobasine group, of which it is a partial synthetic representative. It was obtained for the first time in 1938 (W. Stoll and A. Hofmann).

Lysergic acid produces profound psychic effects in extremely small quantities. Ten to 60 micrograms of the drug is usually enough to produce marked psychic changes, with euphoria, depression and, as reported by Stoll, pupillary changes, alterations in tendon reflexes and visual hallucinations. Although various physiological changes have been attributed to the administration of this substance, no controlled studies on this phase could be found. In an effort to clarify the physiological effects of lysergic acid diethylamide, the following studies were carried out.

PRESENT INVESTIGATION

Material and Methods.—Six male schizophrenic patients were selected on the basis of poor prognosis and failure to respond to other types of therapy. One had been hospitalized for one

From the Ypsilanti State Hospital.
Lysergic acid diethylamide was supplied through the courtesy of Sandoz Chemical Works, Inc., New York.

1. Stoll, W.: Schweiz. Arch. f. Neurol. u. Psychiat. **60**:279, 1947.
2. Condrau, G.: Acta psychiat. et neurol. **24**:9, 1949.
3. Stoll, W.: Schweiz. med. Wchnschr. **79**:110, 1949.

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year; three, for five years; one, for two years, and one, for 34 years. For four of the six patients the diagnosis was paranoid schizophrenia, and for the other two, hebephrenic schizophrenia. A complete physical examination, electroencephalographic and electrocardiographic recordings, blood sugar, nonprotein nitrogen determinations, white blood cell count, hemoglobin determination, urinalysis and cephalin-cholesterol flocculation tests were carried out before the initiation of the experiment and the values found to be within normal limits.

Conditions of Study.—Patients were studied in a room where a trained nurse and physician were in constant attendance. A control period, during which the blood pressure, pulse and respiration rates, deep reflexes, pupillary size and degree of salivation were determined every half-hour, showed no significant alterations in physiological status. Additional control studies were carried out with other substances. Epinephrine hydrochloride in oil, 1 cc., was administered intramuscularly to each of these six patients. The blood pressure and pulse and respiration rates were averaged, and it was determined that the patients acted in the usual manner to this drug.

Lysergic acid diethylamide was administered by mouth in ascending doses, beginning with 0.5 microgram and reaching a maximal of 6 micrograms per kilogram of body weight.

Results.—When the blood pressure responses of these six patients were averaged for each dosage level, the following results emerged: When lysergic acid diethylamide was administered orally in doses up to 6 micrograms per kilogram, it produced a slight rise of blood pressure in all patients. Blood pressure curves were entirely similar during the maximal height of response 2½ hours after administration and returned to normal five or six hours after administration. Although a slight increase in systolic blood pressure was noted, all changes in blood pressure were within normal physiological limits. Except at a dosage level of 2 micrograms per kilogram of body weight, an increase in pulse rate was noted with the administration of increasing amounts of the drug. The maximal increase in pulse rate occurred between one and two hours after administration and gradually declined to pretreatment levels five to six hours after administration. The average pulse rates were always within normal physiological limits, but there was wide variation in individual subjects. One subject showed a depression, and another a decided increase, in the pulse rate after administration of the drug. The extremes, in general, were in the order of 100 per minute as a maximum and 48 as a minimum. Lysergic acid diethylamide in doses up to 6 micrograms per kilogram by mouth does not appear to be a respiratory depressant. There is, on the contrary, a suggestion that it may be a respiratory stimulant, but our present experimental data are too limited to permit formulation of any definite conclusion. For example, with 6 micrograms of lysergic acid diethylamide per kilogram of body weight, one patient showed a respiratory rate of 32 per minute (the highest recorded) and another a respiratory rate of 12 per minute (the lowest recorded).

Administration of lysergic acid diethylamide by mouth in ascending doses up to 6 micrograms per kilogram produced constant flushing responses, which had, however, considerable variation in intensity and duration in different subjects. Duration, as well as rapidity of onset and degree of flushing, seemed to be related to the size of the dose. When the drug was administered by mouth, increased salivation was produced. In no case was dryness of the oral mucous membranes noted. We found, in studying these six patients, that the higher the dose of lysergic acid diethylamide, the greater the salivation response. Individual responses to administration of the drug showed considerable variation in degree but always followed a pattern of quantitative increase in salivation and longer duration of response with increase in dose.

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Contrary to the findings of other investigators, nausea, vomiting and anorexia were not prominent in the present group of patients. In a total of 42 treatments, vomiting was experienced three times. Lysergic acid diethylamide, when administered by mouth in the doses noted, regularly produced dilation of the pupils. As the dose was increased, the reaction to light was progressively impaired in some persons. Maximal pupillary dilation was obtained from two to three hours after administration, the pupillary size gradually returning to normal. The degree of pupillary dilation and duration of this response were directly related to the size of the dose. Conjunctival injection was noted to occur to a varying extent with the lower dosage levels, but with 6 micrograms per kilogram all six patients showed conjunctival injection, which varied only in degree. Increased lacrimation paralleled the increase in dose. With this small series of patients no definite conclusions can be drawn concerning the febrile effects of lysergic acid diethylamide. Two of five patients showed a rise in temperature of 1 degree (F.) when 2 micrograms per kilogram was administered by mouth. Lysergic acid diethylamide produced in these six patients a constant hyperreflexia. The degree of hyperactivity of the knee jerks was directly related to the size of the dose. With 6 micrograms per kilogram, hyperactivity of the deep reflexes was constant in all patients and was present in a far greater degree than when smaller doses were used. The Babinski sign was not observed. There was slight unsteadiness of gait. There was no disturbance of coordination, no past pointing phenomena and no nystagmus. These findings are at variance with those of others, who have noted hypoactive reflexes, nystagmus, ataxia with a positive Romberg sign and past pointing phenomena.

Blood sugar curves without medication showed no significant variation during the fasting period. The responses of these six patients to the administration of 0.5 cc. of epinephrine hydrochloride (1:1,000) was measured by obtaining the blood sugars. The rise in blood sugar was noted 15 minutes after administration of the epinephrine. The level returned to normal, only to rise again to even greater height one hour after administration. These findings are in keeping with the previously determined blood sugar responses to epinephrine in normal subjects. In the present group of patients there was a slight rise in blood sugar beginning with the second or third hour after administration of lysergic acid diethylamide by mouth in a dose of 1 microgram per kilogram of body weight. Average blood sugar values ranged from 91.3 mg. per 100 cc., before administration of the drug, to 97.3 mg. per 100 cc., four hours after administration. With the dose of 1 microgram of the drug per kilogram given by mouth, there was a slight rise in fasting blood sugar, insufficient to permit any conclusion.

Lysergic acid diethylamine when administered in doses of 1 microgram per kilogram produced definite leukocytosis. Provisional conclusions based on this experiment indicate that there is an evaluation of the white blood cell count as a result of administration of the drug (table). The reasons for these alterations are not known.

Lysergic acid when administered in the dose of 1 microgram per kilogram every three to four days for a total of six doses produced no urinary changes. The pretreatment cephalin-cholesterol flocculation tests on all patients gave negative results. During treatment with the lysergic acid these tests continued to give

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negative results. We conclude, therefore, that there is no change in hepatic function as a result of administration of the drug in this amount.

Nonprotein nitrogen values before treatment were within normal limits. Nonprotein nitrogen values during the course of treatment were within normal limits and showed no alteration in individual cases. Immediately after the termination of this experiment nonprotein nitrogen estimates showed no change from pretreatment levels. Six weeks after administration of the last dose of lysergic acid diethylamide nonprotein nitrogen values were likewise normal.

The white blood cell and hemoglobin content were determined before treatment, during treatment, immediately after treatment and six weeks after administration of the last dose of the drug. The pretreatment white blood cell count and hemoglobin content were normal for all patients and remained so during the course of treatment, immediately after treatment and six weeks after treatment. It should be noted that these determinations were made on nontreatment days.

White Blood Cell and Differential Counts with Administration of 1 Microgram of Lysergic Acid Diethylamide per Kilogram

Patient	White Blood Cell Count	Baso-phils	Eosino-phils	Myelo-cytes	Juvenile Forms	Stab Forms	Segmented Forms	Lympho-cytes	Mono-cytes	Degenerated Forms
Before administration										
1	5,800	..	1	..	..	2	74	21	2	..
2	4,950	(differential not done)			..	..	..	..	..	..
3	7,550	1	4	..	..	2	65	22	6	3
4	6,600	..	3	..	..	..	41	53	3	..
5	9,300	1	1	..	2	..	64	29	3	..
Three hours after administration										
1	7,300	2	2	..	..	..	59	36	1	1
2	6,250	1	8	..	..	..	53	38	..	..
3	8,800	..	1	..	..	..	79	19	..	..
4	7,150	1	1	..	..	..	42	56	..	..
5	22,450	..	2	..	..	..	76	22	..	..
Six hours after administration										
1	5,100	1	3	2	..	..	61	33	..	..
2	6,950	..	6	..	..	1	43	50	..	..
3	9,100	2	1	..	..	..	54	39	4	..
4	11,050	2	2	..	1	..	57	36	2	..
5	15,100	..	2	..	..	..	55	38	5	..

Lysergic acid diethylamide as administered had no effect on the weight of five of six patients. One patient showed a gain in weight of 20 pounds (9.1 Kg). Direct instillation of lysergic acid diethylamide into the conjunctival sac (approximately 1 microgram per eye) produced very little effect on the pupils. There was, however, evidence of dilation of slight degree. It becomes evident from this result that pupillary dilation observed during the administration of lysergic acid diethylamide may be due primarily to the central effects of the drug.

Electroencephalographic responses to the administration of 2 micrograms per kilogram of lysergic acid diethylamide were determined. No changes from premedication electroencephalograms could be discerned. In these six patients, who were administered ascending doses of lysergic acid diethylamide, a psychic response, particularly in regard to accessibility, hallucinations, delusions, affectivity and general demeanor, was observed.

When 0.5 microgram of lysergic acid diethylamide per kilogram was administered, definite psychic changes were noted in five of six patients. All changes began one-half to one hour after administration and reached their height two to 2½ hours after administration. These effects gradually subsided, and the patients had returned to their customary psychic status four to five hours after administration

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of the drug. The first changes noted were euphoria, increased spontaneous verbal productivity and alteration from a surly, antagonistic attitude toward the physician to amiability, talkativeness, euphoria and outbursts of laughter. At the height of the reaction patients were laughing in what was felt to be an appropriate manner and were definitely more accessible. One patient showed slight depression between euphoric outbursts. Another became hyperactive, very disturbed and hostile toward the physician, complained of dying and made multiple requests to go home. After the observation period he was noted to be drinking large quantities of water and to be inducing vomiting. A three minute "seizure" occurred in the evening of the same day. During the following night he was incontinent of urine, after which he had an increase in temperature to 100.4 F. and complained of headache. No hallucinations were elicited in this group of patients with the dose indicated.

When 1 microgram of lysergic acid diethylamide per kilogram was administered by mouth, the above observations were confirmed, the effects being greater in degree and more prolonged in duration. Euphoria was prominent. No instance of depression was noted. One patient complained of being worked on by "magic" and expressed the fear that his penis would dry up. He became agitated and complained of "seeing magic." Three of six patients experienced hallucinations with this size of dose. Increased alertness and amiability were observed. When the experiment was repeated with the same size of dose, the same general response was noted. Hallucinations were noted in two of five patients so treated. These were of the "primary" type previously described by others as occurring under the influence of lysergic acid diethylamide.

When 2 micrograms of lysergic acid diethylamide per kilogram was administered by mouth, the same general reaction patterns were observed. Patients were more alert and showed outbursts of euphoria. One patient complained of various unusual somatic sensations. The patients in general were more amiable and more easily accessible. Misidentification of other persons in the environment was noted. Two of five patients admitted to having hallucinations. In one an increased volume of delusional material was noted. Outbursts of infectious laughter were prominent.

When 4 micrograms of lysergic acid diethylamide per kilogram was administered by mouth, the same general reactions were observed. However, these reactions were more prolonged and more intense with the increased dose. Hallucinations were noted in two of six patients.

When 6 micrograms of the drug per kilogram was administered by mouth, the same general reactions were noted. Hallucinations were noted in two of five patients. Psychomotor retardation was in evidence. The patients always maintained relatively good contact with their environment. It should be noted that hallucinations occurred in all patients at some time during these administrations of lysergic acid diethylamide. However, hallucinatory experiences often could not be determined while the patient was under the influence of the drug, but could be elicited some time afterward. In order of frequency, there were first visual hallucinations, consisting of patterns, diagrams and flashes of light, and then paresthesias, with sensations of elongation of the limbs, crawling over the skin and various other somatic sensory disturbances. One patient experienced olfactory hallucinations. Euphoria was prominent in all patients, occurring usually as outbursts, between which patients appeared somewhat disinterested and apathetic.

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Only one patient showed evidence of depression, and then for a short time. Increased accessibility, increased spontaneity, clearer verbal productivity and increase in delusional formulations, increased psychomotor activity and elements of agitation were also noted. Ataxia was not prominent and was seen in only one patient, as evidenced by difficulty in walking and eating with a fork and spoon. No past pointing phenomenon or other disturbances of coordination were observed. The patients were observed particularly in regard to their production of sexually determined material. With the increase of spontaneity noted in these patients as a result of administration of the drug, increased spontaneous sexual material was quite apparent in three patients. One patient, for example, recalled a homosexual episode which he had as a youth and which had not previously been accessible. Another talked about his delusion of having been raped by a monkey, and a third was constantly asking the nurse who was in attendance, "You're my sister; marry me?" Another patient would ask whether the nurse would engage in sexual intercourse. We believe that the increase in accessibility and spontaneity as a result of administration of lysergic acid diethylamide is a general reaction phenomenon and that there are no specific isolated facets of the personality in which retardation or blocking occurs. Although the group of patients is small and the number of treatments limited, it becomes apparent that this increased spontaneity and accessibility is a general psychic reaction; and since sexuality is a part of personality structure, it is only to be expected that sexual material will become more evident with increased spontaneity and productivity.

Two patients who were totally blind, one from methyl alcohol poisoning and the other as a result of a gunshot wound severing the optic nerves, were administered lysergic acid diethylamide to the amount of 1 microgram per kilogram. Their reactions were noted at frequent intervals. Neither patient was manifestly psychotic at the time of administration of the drug. Euphoria and hypersalivation were noted in these patients. One became paranoid, an element which was only in slight evidence before administration of the drug. He denied that he had received any special drug and thought that he had been given only water. He possibly had olfactory hallucinations, or at least misinterpreted stimuli, since he believed that the tobacco smoke which he smelled in the air was really opium. He denied having any visual hallucinations. The second patient became euphoric and showed increased hyperactivity of the deep reflexes and slight dilation of the right pupil. He noted increased lacrimation and slightly increased moisture of the mucous membranes of the mouth. He showed more spontaneous verbalization and denied having any hallucinations. Although this experiment was carried out with only two patients, it was noted that both gave the same general reaction to the drug. There was an increased accessibility, increased euphoria, increased salivation and lacrimation and increased tendon reflexes, but no visual hallucinations, with this dose. It should be noted that both patients had previously had their eye sight and were not congenitally blind.

Because of the increased secretory response noted as a result of administration of lysergic acid diethylamide, the response in the atropinized human subject was determined. These patients were given 1 mg. of atropine sulfate by intramuscular injection 4½ hours prior to the oral administration of 6 micrograms of lysergic acid diethylamide per kilogram. In general, there was slight flushing of the skin in all patients, beginning one to two hours after oral administration of 6 micrograms of

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lysergic acid diethylamide per kilogram. The flushing response was somewhat irregular, but the skin color of most patients had returned to normal six hours after administration. In general, the mucous membranes of the mouth were moist. No drying was noted in any of the patients. One patient showed slightly increased salivation beginning 2½ hours after administration of the drug, and others maintained moist mucous membranes more or less constantly for four to five hours after its administration. The pronounced drying response of this dose of atropine was not maintained when lysergic acid diethylamide was administered subsequently. All patients showed an initial dilation of the pupils, which was increased by the further administration of lysergic acid diethylamide. In general, the maximal pupillary dilation was noted between one and 2½ hours after administration of the drug. Pupillary signs gradually decreased to normal until six hours after administration of lysergic acid diethylamide, after which no effect of either medication was noted.

In general, there was increase in the deep reflexes beginning 1½ hours after administration of the drug, reaching a maximum at approximately two to 2½ hours and gradually declining to normal in six hours. This response was somewhat irregular and varied from patient to patient, but in general there was an increase in deep reflexes, in some patients being very pronounced. The Babinski sign was not elicited. All patients were cooperative during the entire proceeding. All were able to eat the noon meal during the course of the experiment. All patients showed much more spontaneity; euphoric outbursts were prominent. Increased tearing was noted in several. Euphoria seemed to be more prolonged and more sustained than with the same dose of lysergic acid diethylamide without atropine. Hallucinations occurred in most patients, only one failing to have this reaction. Increased accessibility and amiability were noted in all patients. Increased urinary frequency was not observed except in one patient, who during the first hour after administration of lysergic acid diethylamide micturated three times. Slight ataxic phenomena were in evidence but were never so severe as to interfere with the patient's performing such acts as buttoning the clothing, eating, standing, walking and drinking. We concluded from this single experiment with a small group of patients that premedication with atropine decreased the salivation response noted when lysergic acid diethylamide was administered alone. Also to be noted was more persistent euphoria than had been seen previously with this dosage level. Because of the small number of patients, the latter effect cannot be adequately evaluated.

All these six patients were in such poor contact with their environment that very few responses could be elicited in regard to their subjective feelings while under the influence of the drug. One patient felt that his mouth had "cotton in it"; another, that he had been given "magic," and still another complained of a "constriction in my chest." It has been noted that the barbiturates administered to patients under the influence of lysergic acid diethylamide abolish the psychic effects of the latter drug. It is well known that barbiturates initially act on subcortical structures. The site of action of lysergic acid diethylamide is not known. We consider, however, that the drug acts primarily on the cortex to produce a depression, and there is abundant evidence to suggest this, i. e., increased deep reflexes, dilation of the pupils, salivation, euphoria and increased accessibility. One might think of the effects of lysergic acid as being due to a release of the lower centers from cortical control. It would hold, then, that any drug which depresses the subcortical centers would, by blocking the subcortical release effectively, nullify the psychic action of

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lysergic acid diethylamide. This would be further evidence for and support of our present belief that lysergic acid diethylamide in the amounts used acts primarily on the cortex, that the neurological symptoms following administration are directly attributable to this cortical effect and that the psychic phenomena witnessed under its influence are the result of subcortical discharges no longer under the full control of the cortex.

From studies carried out on animals, lysergic acid has been determined to be a relatively nontoxic substance. The lethal intravenous dose was 65 mg. per kilogram and the lethal subcutaneous dose 285 mg. per kilogram in laboratory animals. Our maximum dose was 6 micrograms per kilogram. It would seem therefore that lysergic acid diethylamide is an extremely safe and relatively nontoxic drug.

CONCLUSION

Studies with lysergic acid diethylamide (LSD-25) have been carried out in an effort to clarify the physiological and psychic responses attendant on administration of this drug in schizophrenic patients. The drug produced slight increase in blood pressure, slight increase in pulse rate, no essential change in respiration, increase in salivation and lacrimation, dilation of the pupils, increase in deep reflexes and slight ataxia. Oral administration produced pupillary dilation of marked degree, whereas topical administration produced very slight dilation. The total white blood cell count was increased during the time of action of the drug. Euphoria occurring in outbursts, was prominent. Increased accessibility and amiability, with increased release of libido and greater accessibility of delusional material, was observed. Visual hallucinations of the so-called primary type were not noted in two blind patients treated with the drug but were seen in all of the six patients on whom complete studies were carried out. Urinary constituents, the nonprotein nitrogen level, the electroencephalogram, cephalin-cholesterol flocculation, weight and temperature were not affected by the administration of this drug in doses up to 6 micrograms per kilogram. Lysergic acid diethylamide appears to be a suitable substance for further therapeutic investigation in the psychoses.

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